Remarks

Claims 1 and 2 are pending.

Rejection Under 35 U.S.C. § 112, first paragraph

A. Claims 1 and 2 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor had possession of the claimed invention. The Office action posits that "the specification as originally filed does not support differentially removing proteins from the blood" or "provide a written description that reasonably conveys what Applicants encompass the step of differentially removing." Applicants respectfully disagree and provide examples of places in the specification that indicate possession of the step of differentially removing high molecular weight proteins from the blood.

Applicants discovered that an optimization of blood viscosity (haemorheology) provides a clinical benefit for treating, *inter alia*, ischemia of the foot, and compared two alternative classes of apheresis, i.e., blood separation, methods for accomplishing this goal. Specifically, several plasma differential separation techniques were investigated and compared with plasma exchange therapy. See page 7, lines 25-26 of the specification.

Plasma exchange therapy involves extracting plasma from a blood sample and replacing it with a plasma substitution fluid, such as, for example, 5% albumin or Rheopolyglukin, in order to remove potentially harmful proteins or toxins that may be present in the plasma. However, as pointed out in the specification (page 9, lines 21-23), there are safety drawbacks associated with the requirement of introducing plasma substitution fluids, including the potential transfer of infectious agents such as viruses and prions. Based on Applicants' discovery that optimization of

blood viscosity provides the desired clinical benefit, Applicants provided in the specification differential methods of plasma separation that remove only subsets of the proteins from the plasma and therefore do not require introducing plasma substitution fluids.

Examples of plasma differential separation techniques disclosed in the specification include plasma differential precipitation (see, for example, paragraph bridging pages 9 and 10 of the specification), plasma differential adsorption (see, for example, page 10, lines 10-18 of the specification), and plasma differential filtration (see, for example, page 10, lines 20-26 of the specification). These methods allow for the elimination of plasma proteins according to isoelectric point (pH), surface energy (adsorption affinity), or molecular weight (size). Of these methods, however, only plasma differential filtration will necessarily separate proteins from blood based on molecular weight. The specification provides on page 10, lines 24-26 examples of filter membranes with different pore sizes that can be used to eliminate high molecular weight proteins from the plasma and demonstrates the effectiveness of this method in the Examples.

The specification, therefore, does clearly provide a written description of the claimed method conveying that Applicants were in possession of the claimed method at the time the application was filed. As such, Applicants respectfully request the withdrawal of this rejection.

B. In response to Applicants arguments filed January 16, 2007, the Office action states that "it does not preclude one from having to do undue experimentation to determine what constitutes how to 'differentially' remove protein from the blood." Applicants respectfully point out that avoiding "undue experimentation" is an enablement requirement under 35 U.S.C. § 112, first paragraph and not proper grounds for maintaining the present written description rejection.

However, in order to facilitate prosecution, Applicants submit the following comments in support of the written description and enablement of claims 1 and 2.

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the specification, coupled with information known in the art, without undue experimentation. However, one determines undue experimentation not by analyzing a single factor, but rather by analyzing and weighing many factors. The legal standard set out in *In re Forman* 230 U.S.P.Q. 564, 547 (Bd. Pat. App. & Int. 1986) and elucidated in *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400 (Fed. Cir. 1988) sets forth the following factors for consideration: (1) the quantity of experimentation necessary; (2) the amount of direction or guidance presented; (3) the presence or absence of working examples of the invention; (4) the nature of the invention; (5) the state of the prior art; (6) the relative skill of those in the art; (7) the predictability or unpredictability of the art; and (8) the breadth of the claims.

The specification discloses plasma differential filtration as a means of differentially removing high molecular weight proteins as set forth in claim 1. The nature of the claimed method and the predictability inherent with such apheresis techniques combined with the relatively high skill of those in the art is such that the skilled artisan would be able to apply the exemplified and alternative separation methods alike to alter blood viscosity without undue experimentation.

In the Response to Arguments, the Office action further states "[i]t is not clear that this differentially removing of high molecular weight proteins is only based on the pore size of a filter, since other methods of removing high molecular weight protein may be used." The Office action appears to be suggesting that Applicants are required to provide a description of all

methods of differentially removing high molecular weight proteins. However, that is not the standard for either written description or enablement. The suggestion that there are additional methods available other than filtration based on pore size does not change the fact that Applicants have disclosed a procedure for practicing the claimed method, which satisfies the enablement requirement and demonstrates that Applicants were in possession of the claimed method. In fact, the admission by the Office that other methods of removing high molecular weight protein exist supports the routine nature of these techniques rather than suggesting undue experimentation.

The Office action further states that "it does not preclude one from having to do undue experimentation to determine what constitutes how to 'differentially' remove protein from the blood." However, the specification is clear what is meant by "differentially removing high molecular weight protein." The specification on page 6, lines 5- 16, identifies examples of proteins, which were previously associated with hyperviscosity syndromes, that can be reduced with the claimed method to alter haemorheology. There is no basis to presume that undue experimentation would be required to determine optimal selection parameters for molecular weight in order to achieve the desired haemorheology. The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. *See In re Angstadt,* 537 F.2d 498, 190 USPQ 214 (CCPA 1976).

> The test [for undue experimentation] is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the invention claimed.

PPG Indus., Inc. v. Guardian Indus. Corp., 75 F.3d 1558, 1564, 37 U.S.P.Q.2d 1618, 1623 (Fed. Cir. 1996, internal quotes and citation omitted).

As for the selection of pore size, knowledge in the art relating to the selection of filtration membranes for the filtration of proteins is very high and very predictable. Applicants disclosed a benefit for removing high molecular weight proteins in order to modify the viscosity of the blood and provided that plasma filtration could be used to accomplish this goal. Thus, based on the relative skill of the artisan and knowledge in this field, experimentation to select the appropriate membrane pore size would be both minimal and routine. Thus, a rejection under 35 U.S.C. § 112, first paragraph for an alleged lack of enablement would be inappropriate and should therefore not be submitted by the Office.

Rejection Under 35 U.S.C. § 103

A. Claims 1 and 2 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Georgadze et al, in view of Malchesky et al. The Office action alleges that Georgadze et al. teach that "plasmapheresis may be used for the treatment of ischemia in the lower extremities of diabetics" and that Malchesky et al. teach the "plasmafiltration of blood for the removal of high molecular weight [proteins]." Based on this understanding, the Office action posits that it would have been obvious to modify the method of Georgadze et al. to specifically remove high molecular weight protein as taught by Malchesky et al. since both of these procedures of "plasmapheresis of blood" and "plasmafiltration of blood" are analogous fields of endeavor. Applicants respectfully traverse this rejection on the basis that the Office is using impermissible hindsight to combine these references and that there would have been no reasonable expectation of success that such a combination would arrive at the claimed method.

The Supreme Court reaffirmed the *Graham* factors for determination of obvious under 35 U.S.C. § 103(a). *KSR Int'l Co. v. Teleflex, Inc.* 127 S.Ct. 1727 (2007). The four factual inquiries under *Graham* are:

(a) determining the scope and contents of the prior art;
(b) ascertaining the differences between the prior art and the claims in issue;
(c) resolving the level of ordinary skill in the pertinent art; and
(d) evaluating evidence of secondary consideration.

Graham v. John Deere (*Graham*), 383 U.S. 1, 17-18, 149 USPQ 459, 467 (1966).

The Court has further recognized that the requirement for a teaching, suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings, which was established by the Court of Customs and Patent Appeals, provides a helpful insight for determining whether the claimed subject matter is obvious under 35 U.S.C. § 103(a). In addition, the Court maintained that any analysis supporting a rejection under 35 U.S.C. § 103(a) should be made explicit, and that it is "important to identify reasons that would have prompted a person of ordinary skill in the relevant field to combine the [prior art] elements" in the manner claimed, because "inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known." *KSR* at 1741. Further, the Court, citing *Graham*, indicated that "a factfinder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon *ex post* reasoning. *KSR* at 1742.

Georgadze et al. teaches the use of plasma exchange to extract bacterial toxins, circulating immunocomplexes (CIC), and killer cells associated with diabetic angiopathies. This

is a non-specific removal of the plasma, as discussed above, which must be replaced with a plasma substitution fluid. There is no indication by Georgadze et al. that removal of only high molecular weight proteins would be sufficient to achieve the desired result. Further, there was no teaching that modification of the blood viscosity would have a therapeutic benefit to diabetic ischemia. Malchesky et al. does not correct this deficiency.

Malchesky et al. teaches generally the removal of high molecular weight proteins from blood for the purpose of removing abnormal metabolites or toxins. However, there is no indication in Malchesky et al. that this general approach would have any effect on diabetic ischemia or blood viscosity. As such, there was no teaching, suggestion, or motivation to combine the teachings of Georgadze et al. and Malchesky et al. The Office is using the knowledge provided by the instant application that modifying the viscosity, rather than or in addition to removing any specific toxin or metabolite, would have a therapeutic effect in diabetic ischemia. The Office action is justifying the use of this impermissible hindsight by indicating that the "plasmapherisis" procedures of Georgadze et al. and Malchesky et al. are "analogous fields of endeavor." However, the Office has failed to "identify reasons that would have prompted a person of ordinary skill in the relevant field to combine the [prior art] elements" in the manner claimed. *KSR* at 1741. As such, Applicants respectfully request the withdrawal of this rejection.

B. Claims 1 and 2 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Seidel et al. in view of Georgadze et al. The Office action alleges that Seidel et al. teach an extracorporeal method and apparatus for removing low density lipoproteins using a plasma filter that precipitates low density lipoproteins from blood. Based on this understanding, the Office

action posits that it would have been obvious to use the method of Seidel et al. to treat diabetic patients having ischemia of the foot as taught by Georgadze et al. since both of these blood treatment procedures are analogous fields of endeavor. Applicants respectfully traverse this rejection on the basis that the Office is using impermissible hindsight to combine these references and that there would have been no reasonable expectation of success that such a combination would arrive at the claimed method.

As discussed above, there is no indication by Georgadze et al. that removal of only high molecular weight proteins would be sufficient to achieve the desired result. Further, there was no teaching that modification of the blood viscosity would have a therapeutic benefit to diabetic ischemia. Seidel et al. does not correct this deficiency.

Seidel et al. teaches generally the selective removal of low density lipoprotein from blood by precipitation, i.e., based on isoelectric point at a pH between 5.05 to about 5.25. See column 4, lines 8-16. However, there is no indication in Seidel et al. that this approach would have any effect on diabetic ischemia or blood viscosity. As such, there was no teaching, suggestion, or motivation to combine the teachings of Seidel et al. and Malchesky et al. As above, the Office is using the knowledge provide by the instant application that modifying the viscosity, rather than or in addition to removing any specific toxin or metabolite (including low density lipoprotein), would have a therapeutic effect in diabetic ischemia. Neither reference teaches this. The Office action is justifying the use of this impermissible hindsight by indicating that the "plasmapherisis" procedures of Georgadze et al. and Seidel et al. are "analogous fields of endeavor." However, the Office must "identify reasons that would have prompted a person of ordinary skill in the relevant field to combine the [prior art] elements" in the manner claimed. *KSR* at 1741. Since the

rejection fails to do this, the rejection is improper. As such, Applicants respectfully request the withdrawal of this rejection.

Pursuant to the above amendments and remarks, reconsideration and allowance of the pending application is believed to be warranted. The Examiner is invited and encouraged to directly contact the undersigned if such contact may enhance the efficient prosecution of this application to issue.

A Credit Card Payment authorizing payment in the amount of $60.00, representing the fee for a small entity under 37 C.F.R. § 1.17(a)(1) for a One Month Extension of Time, and a Request for Extension of Time are hereby enclosed. This amount is believed to be correct; however, the Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 14-0629.

Respectfully submitted,

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CERTIFICATE OF EFS-WEB TRANSMISSION UNDER 37 C.F.R. § 1.8

I hereby certify that this correspondence, including any items indicated as attached or included, is being transmitted by EFS-WEB on the date indicated below.

Brian Giles
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9-4-2007
Date